

NON-HODGKIN'S LYMPHOMA AND OTHER CANCERS AMONG A COHORT OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To investigate whether systemic lupus erythematosus (SLE) is associated with non-Hodgkin's lymphoma or other malignant neoplasms.

Methods. Data on a cohort of 1,585 patients with SLE from the nationwide Danish Hospital Discharge Register were linked to information in the Danish Cancer Registry to determine the occurrence of cancer during up to 15 years of followup. The expected number of cancers was calculated from accumulated person-years and national cancer incidence rates.

Results. There was a significant excess of non-Hodgkin's lymphoma among the SLE patients, based on 8 cases observed against 1.5 expected (relative risk [RR] 5.2, 95% confidence interval 2.2-10.3). In addition, a significantly increased RR was found for cancer of the lung (RR 1.9; $n = 15$), the liver (RR 8.0; $n = 5$), and the vagina/vulva (RR 5.7; $n = 3$).

Conclusion. There seemed to be a positive association between SLE and non-Hodgkin's lymphoma. Other cancers with a possible virus-related etiology, such as liver and vaginal/vulva cancer, were also observed in excess. In addition, there was an indication of an increased risk of lung cancer among patients who were hospitalized for SLE.

Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease of unknown etiology, with a prevalence in Scandinavia of 1 in 2,800 persons (1). The disease is much more common among

women than among men, particularly in the age group 15-64 years (2), which suggests that hormonal factors may be involved. Genetic and environmental factors may also be important (2).

The clinical picture often demonstrates multi-organ involvement, including various combinations of skin rashes, arthritis, vasculitis, renal manifestations, and central nervous system abnormalities, but any organ or tissue may be involved. B lymphocyte activation is an essential element in the pathogenesis of SLE, leading to production of a wide variety of autoantibodies, most of which are organ nonspecific and are directed against nuclear antigens (3,4). Abnormalities of the T lymphocyte system also seem to be present. Some autoantibodies may be directly pathogenic, but often they are part of immune complexes, and many clinical manifestations are a consequence of the deposition of such complexes (5).

A large number of case reports has described the association between SLE and lymphoproliferative cancer, especially non-Hodgkin's lymphoma (6-13). These clinical observations are, however, supported by only a single cohort study of cancer incidence, in which a limited number of patients was investigated (14). Mortality surveys and survival studies have reported a very small number of deaths from lymphoproliferative malignancies (15) or malignancies in general (16-19) among SLE patients. Therefore, these studies provide no definitive evidence of an association with SLE. In followup reports from several small clinical series, none of which included the expected number of cancers (20-25), the finding of 3 lymphoproliferative cancers was the largest number identified among 485 patients followed up for 20 years (22). Overall, previous investigations provided only limited support for an association between SLE and lymphoproliferative cancers.

Apart from the postulated association with lymphoproliferative malignancies, little is known about the occurrence of other types of cancer among patients with

Supported by grant MAO NO1-CP-85639-04 from the National Cancer Institute.

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Submitted for publication October 11, 1996; accepted in revised form October 15, 1996.

SLE. We therefore carried out a linked registry study of 1,585 patients with SLE in order to investigate the risk for non-Hodgkin's lymphoma and other types of cancer.

PATIENTS AND METHODS

The Hospital Discharge Register, the Central Population Register, and the Cancer Registry in Denmark were linked in order to establish and follow up a cohort of SLE patients for occurrence of cancer over a period of 15 years.

Since 1977, the Hospital Discharge Register has kept records of more than 99% of all discharges from Danish hospitals (26). The information on every discharge includes a personal identification number, the date of discharge, and up to 20 diagnoses. During the study period, diagnoses were coded according to a Danish version of the International Classification of Diseases, eighth revision (ICD-8) (27). The vital status of all citizens in Denmark is recorded in the Central Population Register, together with the personal identification number, and this offers the opportunity for obtaining dates of death or emigration. The Cancer Registry receives notifications on all cases of cancer in Denmark, including papillomas of the lower urinary tract and benign tumors of the nervous system and meninges. In addition, *in situ* carcinoma and epithelial dysplasia of the cervix uteri, diagnosed at biopsy or in more than 1 smear test, are also reported to the Cancer Registry (28). These conditions are classified according to the cervical intraepithelial neoplasia classification (29). The completeness of cancer registration in Denmark has been estimated to be 97.8% for one type of invasive cancer (30).

From the Hospital Discharge Register, we identified 1,667 patients who were hospitalized during 1977-1989 with a discharge diagnosis of SLE (ICD-8 code 734.19). Information was also extracted from the Register about all other hospitalizations that occurred and that were recorded before and after the hospitalization that first listed a discharge diagnosis of SLE, thus providing a full hospitalization history for each individual. After linkage with the Central Population Register, 1,585 patients remained in the study group; 14 patients (0.8%) had an invalid identification number and 68 patients (4%) died during the hospitalization for SLE.

All 1,585 patients were followed up for occurrence of cancer from the date of first known discharge diagnosis of SLE until the date of death or emigration or to the end of December 1991. The followup was facilitated by using the personal identification number of each patient to combine the information contained in the Central Population Register with the Cancer Registry data. Date of first known discharge was used as the entry date. However, an unknown proportion of patients will have been diagnosed with SLE some time before this date. The expected number of cancers was calculated on the basis of national incidence rates, by sex, age, and calendar-time in 5-year intervals. Multiplication of person-years under observation by the incidence rates yielded the number of cancers that would be expected if patients with SLE experienced the same risk as that prevailing in the general population of Denmark. Tests of significance and 95% confidence intervals (95% CI) for the relative risk (RR) (i.e., the ratio of observed-to-expected cancers) were computed based on the assumption that the observed number of cases in a specific

Table 1. Characteristics of 1,585 patients discharged with systemic lupus erythematosus

Variable	No. (%) men	No. (%) women
Total	277 (17)	1,308 (83)
Length of followup, years		
<1	32 (12)	104 (8)
1-4	105 (38)	419 (32)
5-9	78 (28)	409 (31)
10-15	62 (22)	376 (29)
Year of entry to the cohort		
1977-1980	133 (48)	551 (42)
1981-1984	60 (22)	341 (26)
1985-1989	84 (30)	416 (32)
Age at entry to the cohort, years		
0-39	67 (24)	492 (38)
40-59	102 (37)	432 (33)
60+	108 (39)	384 (29)

category followed a Poisson distribution. Exact Poisson limits were used when the observed number was <10; otherwise, Byar's approximation was used (31).

Medical records were obtained for a subgroup of patients who were diagnosed with non-Hodgkin's lymphoma during followup, in order to confirm the SLE diagnosis and the date of diagnosis, and to search for information about medical therapy and presence of secondary Sjögren's syndrome. In addition, medical records were traced for those patients who were identified with lung cancer during followup, in order to explore whether there was any misclassification of SLE with other connective tissue diseases, in particular, rheumatoid arthritis or systemic sclerosis, which have also been associated with lung cancer.

RESULTS

The cohort of 1,585 SLE patients consisted of 83% women and 17% men. The average length of followup was 6.8 years, with a total of 10,807 person-years accrued during a maximum of 15 years followup. Other cohort characteristics are given in Table 1.

The overall cancer incidence was significantly increased by 30% in the SLE patients compared with that in the general population (Table 2). This increase was mainly due to an excess of non-Hodgkin's lymphoma, primary liver cancer, lung cancer, and other, unspecified female genital cancer (2 cases of squamous cell carcinoma of the vagina and 1 case of squamous cell carcinoma of the vulva). In addition, we observed 1 patient with mycosis fungoides, 1 with chronic lymphocytic leukemia (RR 1.6, 95% CI 0.0-8.8), and 2 with acute non-lymphocytic leukemia (RR 3.6, 95% CI 0.4-12.9). No cases of Kaposi's sarcoma were observed.

Exclusion of the first year of followup reduced the RR for non-Hodgkin's lymphoma to a 3.6-fold

Table 2. Observed (Obs) and expected (Exp) numbers and relative risks (RR) of cancer at different sites among 1,585 patients with systemic lupus erythematosus*

Cancer site (ICD-7 codes)	Obs	Exp	RR	95% CI
All malignant neoplasms (140-205)	102	78.5	1.30	1.06-1.58
Buccal cavity and pharynx (140-148)	1	1.2	0.9	0.0-4.7
Digestive organs (150-159)	19	16.6	1.1	0.7-1.8
Esophagus (150)	1	0.5	2.0	0.0-10.9
Stomach (151)	2	2.0	1.0	0.1-3.6
Colo-rectum (153-154)	10	9.5	1.1	0.5-1.9
Liver (155)	5	0.6	8.0	2.6-18.6
Pancreas (157)	1	2.2	0.5	0.0-2.5
Respiratory organs (160-164)	17	8.8	1.9	1.1-3.1
Larynx (161)	2	0.5	4.0	0.5-14.3
Lung (162)	15	8.0	1.9	1.1-3.1
Breast (170)	14	14.0	1.0	0.5-1.7
Cervix uteri (171)	2	2.8	0.7	0.1-2.5
Corpus uteri (172)	4	3.3	1.2	0.3-3.1
Ovary (175)	0	3.0	-	-
Other and unspecified female genital organs (176)	3†	0.5	5.7	1.2-16.6
Prostate (177)	1	1.7	0.6	0.0-3.3
Kidney (180)	1	1.9	0.5	0.0-2.9
Urinary bladder (181)	5	3.1	1.6	0.5-3.7
Melanoma (190)	1	2.0	0.5	0.0-2.7
Non-melanoma skin cancer (191)	10	10.1	1.0	0.5-1.8
Brain and nervous system (193)	3	2.0	1.5	0.3-4.3
Non-Hodgkin's lymphoma (200, 202)	8	1.5	5.2	2.2-10.3
Hodgkin's disease (201)	1	0.3	3.8	0.1-21
Multiple myeloma (203)	1	0.7	1.4	0.0-7.7
Leukemia (204)	3‡	1.5	2.0	0.4-5.7
Mycosis fungoides (205)	1	0.0	34.1	0.9-190
Other specified and unspecified sites (173-174, 178-179, 192, 194-197, 199)	3	2.1	1.4	0.3-4.1
Metastases with unknown primary site (198)	4§	1.1	3.7	1.0-9.5

* ICD-7 = International Classification of Diseases, seventh revision (28); 95% CI = 95% confidence interval.

† Two cases of squamous cell carcinoma of the vagina and 1 case of squamous cell carcinoma of the vulva.

‡ Two cases of acute myeloid leukemia and 1 case of chronic lymphocytic leukemia.

§ One adenocarcinoma (unspecified site), 1 adenosquamous carcinoma (peritoneum), 1 squamous cell carcinoma (head and neck), and 1 carcinoma not otherwise specified (brain).

increase ($n = 5$; 95% CI 1.2-8.6), but did not change the RR substantially for primary liver cancer ($n = 5$; RR 7.9, 95% CI 2.6-18.6), lung cancer ($n = 12$; RR 1.7, 95% CI 0.9-3.0), or cancer of other female organs ($n = 3$; RR 6.5, 95% CI 1.3-19.0).

A high RR for non-Hodgkin's lymphoma, observed during the first year of followup, persisted after 10 years of followup (Table 3). The RR according to age at cancer diagnosis decreased with increasing age. Detailed information from the medical records for the 8 SLE patients with non-Hodgkin's lymphoma is given in Table 4. For all lymphoma cases, the clinicians gave a diagnosis of SLE, although 1 patient (patient 4) fulfilled only 3 of the American College of Rheumatology (ACR) criteria (32). SLE was, on average, diagnosed 6 years (range 0-15 years) before the first known hospitalization with SLE. All patients except 1 had been treated with glucocorticoids and 2 patients were treated with azathioprine in addition to steroids (1 of these was also given

alkylating agents). Secondary Sjögren's syndrome was present in 2 patients. Six of the non-Hodgkin's lymphoma cases were nodal and 2 were extranodal; none of the latter were cerebral lymphomas. Patient 3 had non-Hodgkin's lymphoma in the tonsil, which was followed 14 years later by a diagnosis of SLE. A second primary non-Hodgkin's lymphoma was identified in the testis of this patient 6.5 years after the SLE diagnosis.

The observed cases of primary liver cancer occurred after 1-9 years of followup, and the patients were all more than 60 years old at the time of the cancer diagnosis (Table 3). Two of the 3 patients with hepatocellular carcinoma had diagnoses of liver cirrhosis recorded in the Hospital Discharge Register ~10 years prior to the cancer diagnosis; 1 of these patients had hepatitis in addition to cirrhosis 12 years prior to the cancer. Liver cirrhosis was also diagnosed in 1 patient with an unspecified histologic type of hepatic carcinoma, but the 2 hepatic conditions occurred at the same

Table 3. Observed (Obs) and expected (Exp) numbers and relative risks (RR) of non-Hodgkin's lymphoma, liver cancer, and lung cancer according to sex, length of followup, and age at cancer diagnosis*

Variable	Non-Hodgkin's lymphoma				Liver cancer				Lung cancer			
	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
Sex												
Male	3	0.3	9.4	1.9-27	2	0.2	11.5	1.4-42	5†	3.0	1.7	0.5-3.9
Female	5	1.2	4.1	1.3-9.6	3	0.5	6.6	1.4-19	10‡	5.0	2.0	1.0-3.7
Length of followup, years												
<1	3	0.2	16.8	3.5-49	0	0.1	-	-	3	1.0	3.0	0.6-8.9
1-4	1	0.6	1.6	0.0-8.7	3	0.3	10.7	2.2-31	4	3.4	1.2	0.3-3.0
5-9	2	0.5	3.9	0.5-14.0	2	0.2	10.1	1.1-36	3	2.7	1.1	0.2-3.3
10-15	2	0.2	10.1	1.2-36	0	0.1	-	-	5§	0.9	5.6	1.8-13.2
Age at cancer diagnosis, years												
0-39	1	0.1	12.8	0.3-17.5	0	0.0	-	-	0	0.1	-	-
40-59	3	0.4	8.1	1.7-24	0	0.1	-	-	5¶	2.0	2.5	0.8-5.9
60+	4	1.1	3.7	1.0-9.4	5	0.5	9.9	3.2-23	10	5.9	1.7	0.8-3.1

* 95% CI = 95% confidence interval.

† Three squamous cell carcinomas, 1 adenocarcinoma, and 1 large cell carcinoma.

‡ Four small cell carcinomas and 6 adenocarcinomas.

§ Two small cell carcinomas and 3 adenocarcinomas.

¶ Three adenocarcinomas, 1 small cell carcinoma, and 1 large cell carcinoma.

hospitalization. One patient with cholangiocarcinoma had several liver diagnoses, including cirrhosis (possibly primary biliary cirrhosis), diagnosed 2 years before the carcinoma, and lupoid hepatitis, diagnosed a few months before the carcinoma.

The validation of the SLE diagnosis among the 15 cases of lung cancer, based on medical records, showed that 6 patients fulfilled the ACR criteria, 2 patients fulfilled only 2-3 criteria, while 3 patients probably had discoid lupus erythematosus. None of these patients, however, had signs of rheumatoid arthritis or systemic sclerosis. Two patients with lung cancer, diagnosed after 0.5 years and 2.0 years of followup, most likely had paraneoplastic syndrome that was misinterpreted as SLE. For the remaining 2 lung cancer patients, information about diagnostic criteria behind the SLE diagnosis could not be validated (medical records could not be traced). The RR for lung cancer after 10 or more years of followup, which was not influenced by the cases with paraneoplastic syndrome, was particularly high based on the occurrence of lung cancer in 5 patients, of whom 1 had discoid lupus erythematosus (Table 3). Three of these 5 lung cancers were adenocarcinomas (RR 10.9, 95% CI 1.2-39 during 10-15 years of followup) and 2 were small cell carcinomas (RR 11.7, 95% CI 2.3-34).

Squamous cell carcinomas in female genitals occurred 1 year (vagina), 8 years (vulva), and 11 years (vagina) after the first known hospitalization with SLE among women ages 66, 24, and 33 years, respectively, at cancer diagnosis. The woman diagnosed at age 66 with

cancer of the vagina had a squamous cell carcinoma of the cervix 20 years prior to the vaginal neoplasm. Although the number of invasive cervical cancers observed was less than expected, the RR for cervical intraepithelial lesions was increased, with the majority of cases occurring during the first 1-4 years of followup (Table 5).

DISCUSSION

The present study shows that patients with SLE experience an increased risk for non-Hodgkin's lymphoma. In addition, we observed excesses of cancer of the liver, lung, and vagina/vulva that have not been reported previously. Risk elevation for cervical intraepithelial neoplasia was confined to 1-4 years after the first SLE hospitalization.

The number of patients included in the present study is about 3 times larger than that included in any earlier cancer incidence study of SLE (21) and considerably larger than the only previous study reporting both the observed and the expected number of cancers (14). The quality of the outcome assessment was notably high, since this was based on information in a nationwide registry with thorough notification procedures (28). When patients with a chronic disease such as SLE are identified through a Hospital Discharge Register, a substantial proportion of cases are likely to be prevalent at the time of first known hospitalization with SLE. One effect of mixing prevalent and incident cases of SLE in our study is that the time lag between SLE and cancer is,

Table 4. Description of 8 systemic lupus erythematosus (SLE) patients with non-Hodgkin's lymphoma (NHL) according to information given in the medical record and in the Cancer Registry*

Patient/sex/age at SLE diagnosis	SLE criteria met	Treatment for SLE	Histopathology for NHL (ICD-O morphology)	NHL type	Time between diagnosis of SLE and NHL, years	Comments
1/M/68	Arthritis, pleuritis, proteinuria, positive LE cell preparation	Glucocorticoids	NOS	Nodal	2.5†	None
2/M/73	Pleuritis, proteinuria, anti-DNA, ANA	Glucocorticoids, azathioprine, cyclophosphamide, melphalan	Immunoblastic type	Nodal	6.0	Start of therapy prior to NHL: azathioprine 5.5 years (duration 0.5 years); cyclophosphamide 5 years (duration 2.5 years); melphalan 2.5 years (duration 2.5 years)
3/M/63	Arthritis, positive LE cell preparation, ANA, leukopenia	Glucocorticoids	Centroblastic type, NOS (second primary NHL)	Extranodal (testis)	6.5	NHL (tonsil) 14 years prior to SLE, treated with radiation
4/F/42	Arthritis, positive LE cell preparation, ANA	Glucocorticoids	Immunocytoma	Extranodal (connective tissue)	6.5	None
5/F/52	Arthritis, pleuritis, positive LE cell preparation, anti-DNA, ANA	Glucocorticoids	NOS	Nodal	15†	Secondary Sjögren's syndrome at age 52
6/F/40	Malar rash, discoid rash, photosensitivity, arthritis, pericarditis, ANA	Glucocorticoids, azathioprine	NOS	Nodal	16	Secondary Sjögren's syndrome at age 43; therapy with azathioprine started 13 years prior to NHL (duration 13 years)
7/F/27	Malar rash, discoid rash, anti-DNA, false-positive serologic test for syphilis, ANA	Hydroxychloroquine	Follicular center cell, cleaved, follicular	Nodal	16-18†	None
8/F/20	Photosensitivity, arthritis, pericarditis, ANA	Glucocorticoids	Centroblastic type, NOS	Nodal	19	None

* Diagnosis of SLE was made according to the 1982 American College of Rheumatology criteria (32). ICD-O = International Classification of Diseases for Oncology; LE cell = lupus erythematosus cell; NOS = not otherwise specified; ANA = antinuclear antibodies.

† Cases observed within 1 year from first known hospitalization with SLE.

in some cases, longer than indicated by our data. Patients diagnosed and treated at outpatient clinics were not included in the cohort and, therefore, the study population most probably comprised patients with more severe forms of SLE. Thus, the findings may only be applicable to this subgroup of patients with SLE, who probably differ from the total SLE population in several aspects, e.g., a larger proportion may be treated with immunosuppressive agents that have potential side effects, including effects on cancer risk. Within the scope of the present study, it was impossible to obtain information about medical treatment of the entire SLE cohort; this was done only for those who developed non-Hodgkin's lymphoma during followup.

Misclassification in relation to the SLE diagnosis

Table 5. Observed (Obs) and expected (Exp) number and relative risks (RR) for cervical precancerous lesions according to the cervical intraepithelial neoplasia (CIN) classification among 1,308 women with systemic lupus erythematosus*

Variable	All CIN				CIN III†			
	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
Total	25	12.4	2.0	1.3-3.0	18	8.1	2.2	1.3-2.5
Length of followup, years								
<1	2	1.4	1.4	0.2-5.0	2	1.0	2.0	0.2-7.2
1-4	17	5.4	3.1	1.8-5.0	11	3.6	3.0	1.5-5.4
5-9	4	4.0	1.0	0.3-2.6	3	2.5	1.2	0.2-3.4
10-15	2	1.5	1.3	0.2-4.7	2	1.0	2.0	0.2-7.3

* See ref. 29 for a description of the CIN. 95% CI = 95% confidence interval.

† Severe dysplasia and in situ carcinoma.

may occur, especially since SLE patients present with many different symptoms, and differentiation between SLE and other connective tissue diseases can be difficult in some clinical situations (5). Differential misclassification might have been a concern in relation to primary Sjögren's syndrome, rheumatoid arthritis, and systemic sclerosis, all of which are known to be associated with non-Hodgkin's lymphoma (33-35) and/or lung cancer (33,34,36). However, for the subsets of SLE patients with non-Hodgkin's lymphoma and lung cancer, the medical record review gave no evidence of such diagnoses. If the misclassified disease is unrelated to cancer, such random misclassification tends to underestimate the association between SLE and cancer.

Selection bias may be present if SLE patients are hospitalized because of symptoms of a cancer. In relation to non-Hodgkin's lymphoma, selection bias could be suspected because the risk was particularly high during the first year of followup. This unequal distribution of cases over time indicates that the overall risk estimate may be overestimated due to a greater probability of selecting those with both SLE and lymphoma into the cohort compared with the probability of selecting those with SLE only. However, after exclusion of the first year subsequent to the SLE hospitalization, the RR for non-Hodgkin's lymphoma was still significantly elevated. Two lung cancer patients were selected into the SLE cohort because a paraneoplastic syndrome was misinterpreted as SLE. The presence of these patients clearly represents a selection bias that tends to inflate the overall RR for lung cancer.

Numerous case reports have called attention to the co-occurrence of SLE and non-Hodgkin's lymphomas (6-10,12,13). The only previous followup study showing a significant increase in the risk of non-Hodgkin's lymphoma was a recent Finnish study (14) that showed an RR of 44 for non-Hodgkin's lymphoma among 182 women with SLE, on the basis of 4 cases. The finding that non-Hodgkin's lymphoma was the only lymphoproliferative cancer observed in excess in the present study may suggest that the association is quite specific, and perhaps the clinical feature of SLE responsible for the excess was a relative immunodeficiency state. However, alternative explanations or possible confounders for the association between SLE and non-Hodgkin's lymphoma may be treatment with immunosuppressive agents (37) or coexistence of Sjögren's syndrome (35); these factors were present among 3 lymphoma patients. The presence of secondary Sjögren's syndrome may, however, be underestimated, be-

cause symptoms of the syndrome may quite frequently be overlooked.

It is noteworthy that some SLE patients with non-Hodgkin's lymphoma showed an atypical SLE presentation (mainly, 3 male patients of ages 63-73 years at SLE diagnosis). Furthermore, 1 of these patients had 2 forms of lymphoma, with SLE being recognized in between the 2 lymphoma diagnoses, suggesting some overlap between the disease entities. A common feature is exaggerated lymphocyte stimulation, and, in animal models of SLE, a benign lymphoproliferation often evolves to malignant lymphoma (38). SLE and non-Hodgkin's lymphoma may be the manifestations of the same underlying defect, perhaps involving virus infection in a genetically or immunologically susceptible individual (39). This susceptibility may be comparable to the immunosuppressed state, seen among organ-transplant recipients or patients with acquired immunodeficiency syndrome, which predisposes to non-Hodgkin's lymphoma (40,41) possibly due to infection with Epstein-Barr virus.

Susceptibility to another type of virus, human papillomavirus (HPV), may be related to the excess of cancer of the vagina/vulva observed in the present study (42). However, cervical cancer is thought to be most strongly related to HPV infection (43), and was not increased in incidence. In immunosuppressed transplant patients, the incidence of vulva/vaginal cancer is also increased, as is cervical cancer (40). Premalignant lesions of the cervix were observed in excess only during the time interval 1-4 years after the SLE hospitalization. This finding may reflect increased medical surveillance among women hospitalized with SLE or may be due to chance. An excess of cervical intraepithelial neoplasia (44) or atypia of the cervix (45) has been described in 2 reports of SLE.

Primary liver cancer may be connected to hepatitis B or hepatitis C infection (46). Viral hepatitis may have played a role in 1 case of primary liver cancer in our investigation. It is worth noting that 4 of 5 liver cancer patients also had a diagnosis of liver cirrhosis in the Hospital Discharge Register. In 1 of these patients, it could not be established whether the patient really had SLE, or had lupoid hepatitis, or had both. Whatever the relation, the concomitant diagnosis of liver cirrhosis may have influenced the increased incidence of liver cancer, which is consistent with the results of a recent Swedish study (47).

The overall risk estimate for lung cancer presented herein must be interpreted with caution due to the initial selection bias described previously. However,

the 6-fold increase in lung cancer risk seen after 10 or more years of followup indicates that a genuine association may exist. Excess of lung cancer seems to be a general feature of connective tissue diseases such as rheumatoid arthritis (33,34), systemic sclerosis (36), and, possibly, SLE, all of which may be characterized by lung involvement, and fibrosis is a common element (affecting up to 9% of SLE patients [48]) that may increase the risk of lung cancer.

The cancer pattern observed among SLE patients is, to some degree, consistent with the pattern seen among transplant patients, and virus is implicated in the etiology of these overlapping cancers (non-Hodgkin's lymphoma, vulva/vagina cancer, and liver cancer) (41). When the cancer pattern in SLE is compared with that observed in patients with other autoimmune diseases, it is worth noting that an excess of non-Hodgkin's lymphoma is also seen in both rheumatoid arthritis and Sjögren's syndrome patients (33-35), while an excess of lung cancer may be a common feature for SLE, rheumatoid arthritis, and systemic sclerosis, as previously mentioned (33,34,36).

Our study provides further evidence, based on nationwide hospitalization data, to support the presumption of an increase in the risk of non-Hodgkin's lymphoma among patients with SLE. Additional studies are needed to clarify the cause(s) and mechanisms that link SLE and non-Hodgkin's lymphoma, especially the importance of immunosuppressive therapy and the coexistence of Sjögren's syndrome. Particular attention should be paid to resolving the relevance of the atypical presentation of SLE, and clinicians should be extra alert both to the presence of non-Hodgkin's lymphoma and to the possibility of paraneoplastic syndromes in such patients. The finding of excesses of other cancers, such as liver and vagina/vulva cancer and, possibly, lung cancer, among patients with SLE also calls for further investigation.

ACKNOWLEDGMENTS

We thank Joseph F. Fraumeni, Jr., at the National Cancer Institute (Bethesda, Maryland) for helpful comments on the manuscript and Andrea Bautz at the Danish Cancer Society (Copenhagen, Denmark) for computer assistance.

REFERENCES

- Nived O, Sturfelt G, Wollheim F: Systemic lupus erythematosus in an adult population in southern Sweden: incidence, prevalence and validity of ARA revised classification criteria. *Br J Rheumatol* 24:147-154, 1985
- Hochberg MC: Systemic lupus erythematosus. *Rheum Dis Clin North Am* 16:617-639, 1990
- Tsokos GC: Overview of cellular immune function in systemic lupus erythematosus. In: *Systemic Lupus Erythematosus*. Edited by RG Lahita. New York, Churchill Livingstone, 1992
- Shefner R, Manheimer-Lory A, Davidson A, Paul E, Aranow C, Katz J, Diamond B: Idiotypes in systemic lupus erythematosus: clues for understanding etiology and pathogenicity. *Chem Immunol* 48:82-108, 1990
- Goust J-M, Tsokos G: Systemic lupus erythematosus. *Immunol Ser* 58:437-449, 1993
- Green JA, Dawson AA, Walker W: Systemic lupus erythematosus and lymphoma. *Lancet* ii:753-755, 1978
- Sugai S, Tachibana J, Sawada M, Shimizu S, Hirose Y, Takiguchi T, Konda S: Malignant lymphomas in patients with autoimmune diseases: a report of 6 cases and a review of the Japanese literature. *Jpn J Med* 26:339-347, 1987
- Posner MA, Gloster ES, Bonagura VR, Valacer DJ, Ilowite NT: Burkitt's lymphoma in a patient with systemic lupus erythematosus. *J Rheumatol* 17:380-382, 1990
- Kaji T, Inose K, Tsuchida A, Andoh K, Ohkubo Y, Ono K, Murakami H, Yano S, Omine M, Naruse T, Kojima M, Joshita T, Suchi T: T-zone lymphoma in association with systemic lupus erythematosus. *J Med* 22:225-241, 1991
- Houssiau FA, Kirkove C, Asherson RA, Hughes CRV, Timothy AR: Malignant lymphoma in systemic rheumatic diseases: a report of five cases. *Clin Exp Rheumatol* 9:515-518, 1991
- Efremidis A, Eiser AR, Grishman E, Rosenberg V: Hodgkin's lymphoma in an adolescent with systemic lupus erythematosus. *Cancer* 53:142-146, 1984
- Wyburn-Mason R: SLE and lymphoma (letter). *Lancet* i:156, 1979
- Asherson RA, Block S, Houssiau A, Hughes RV: Systemic lupus erythematosus and lymphoma: association with an antiphospholipid syndrome. *J Rheumatol* 18:277-279, 1991
- Pettersson T, Pukkala E, Teppo L, Friman C: Increased risk of cancer in patients with systemic lupus erythematosus. *Ann Rheum Dis* 51:437-439, 1992
- Oleinick A: Leukemia or lymphoma occurring subsequent to an autoimmune disease. *Blood* 29:144-153, 1967
- Uрман JD, Rothfield NF: Corticosteroid treatment in systemic lupus erythematosus: survival studies. *JAMA* 238:2272-2276, 1977
- Karsh J, Klippel JH, Balow JE, Decker JL: Mortality in lupus nephritis. *Arthritis Rheum* 22:764-769, 1979
- Wallace DJ, Podell T, Weiner J, Klinenberg JR, Forouzes S, Dubois EL: Systemic lupus erythematosus—survival patterns: experience with 609 patients. *JAMA* 245:934-938, 1981
- Rosner S, Ginzler EM, Diamond HS, Weiner M, Schlesinger M, Fries JF, Wasner C, Medsger TA Jr, Ziegler G, Klippel JH, Hadler NM, Albert DA, Hess EV, Spencer-Green G, Grayzel A, Worth D, Hahn BH, Barnett EV: A multicenter study of outcome in systemic lupus erythematosus. II. Causes of death. *Arthritis Rheum* 25:612-617, 1982
- Canoso JJ, Cohen AS: Malignancy in a series of 70 patients with systemic lupus erythematosus. *Arthritis Rheum* 17:383-390, 1974
- Lewis RB, Castor CW, Knisley RE, Bole GG: Frequency of neoplasia in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 19:1256-1260, 1976
- Black KA, Zilko PJ, Dawkins RL, Armstrong BK, Mastaglia GL: Cancer in connective tissue disease. *Arthritis Rheum* 25:1130-1133, 1982
- Sulkes A, Naparstek Y: The infrequent association of systemic lupus erythematosus and solid tumors. *Cancer* 68:1389-1393, 1991
- Lopez-Dupla M, Khamashta M, Pintado-Garcia V, Lavilla-Uriol P, Valencia-Ortega E, Gil-Aguado A: Malignancy in systemic lupus erythematosus: a report of five cases in a series of 96 patients. *Lupus* 2:377-380, 1993
- Menon S, Snaith ML, Isenberg DA: The association of malignancy

- with SLE: an analysis of 150 patients under long-term review. *Lupus* 2:177-181, 1993
26. Danish National Board of Health: The Activity in the Hospital Care System. Copenhagen, Danish National Board of Health, 1981
 27. Danish National Board of Health: Classification of Diseases. Copenhagen, Danish National Board of Health, 1976
 28. Storm HH, Pihl J, Michelsen E, Nielsen AL: Cancer incidence in Denmark 1993. Copenhagen, Danish Cancer Society, 1996
 29. Richart RM: Cervical intraepithelial neoplasia. *Pathol Annu* 8:301-328, 1973
 30. Storm HH: Completeness of cancer registration in Denmark 1943-1966 and efficacy of record linkage procedures. *Int J Epidemiol* 17:44-49, 1988
 31. Rothman KJ, Boice JD: Epidemiologic analysis with a programmable calculator. DHHS Publication No. (NIH) 79-1649. Washington, DC, US Government Printing Office, 1979
 32. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271-1277, 1982
 33. Gridley G, McLaughlin JK, Ekblom A, Klareskog L, Adami H-O, Hacker DG, Hoover R, Fraumeni JF Jr: Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 85:307-311, 1993
 34. Isomäki HA, Hakulinen T, Joutsenlahti U: Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chronic Dis* 31:691-696, 1978
 35. Kassan SS, Thomas TL, Moutsopoulos HM, Hoover R, Kimberly RP, Budman DR, Costa J, Decker JL, Chused TM: Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 89:888-892, 1978
 36. Rosenthal AK, McLaughlin JK, Linet MS, Persson I: Scleroderma and malignancy: an epidemiological study. *Ann Rheum Dis* 52:531-533, 1993
 37. Kinlen LJ, Sheil AGR, Peto J, Doll R: Collaborative United Kingdom-Australian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 2:1461-1466, 1979
 38. Theofilopoulos AN: Murine models of lupus. In: *Systemic Lupus Erythematosus*. Edited by RG Lahita. New York, Churchill Livingstone, 1992
 39. Laurence J, Wong JEL, Nachman R: The cellular hematology of systemic lupus erythematosus. In: *Systemic Lupus Erythematosus*. Edited by RG Lahita. New York, Churchill Livingstone, 1992
 40. Birkeland SA, Storm HH, Lamm IU, Barlow L, Blohme I, Forsberg B, Eklund B, Fjeldborg O, Friedberg M, Frödin L, Glattre E, Halvorsen S, Holm NV, Jakobsen A, Jørgensen HE, Ladefoged J, Lindholm T, Lundgren G, Pukkala E: Cancer risk after renal transplantation in the Nordic countries, 1964-1986. *Int J Cancer* 60:183-189, 1995
 41. Kinlen LJ: Immunosuppression and cancer. In: *Mechanisms of Carcinogenesis in Risk Identification*. Edited by H Vainio, PN Magee, DB McGregor, AJ McMichael. Lyon, International Agency for Research on Cancer, 1992
 42. Daling JR, Sherman KJ: Relationship between human papillomavirus infection and tumours of anogenital sites other than the cervix. *IARC Sci Publ* 119:223-241, 1992
 43. Schiffman MH, Bauer HM, Hoover RN, Glass AG, Cadell DM, Rush BB, Scott DR, Sherman ME, Kurman RJ, Wacholder S, Stanton CK, Manos MM: Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. *J Natl Cancer Inst* 85:958-964, 1993
 44. Nyberg G, Eriksson O, Westberg NG: Increased incidence of cervical atypia in women with systemic lupus erythematosus treated with chemotherapy. *Arthritis Rheum* 24:648-650, 1981
 45. Blumenfeld Z, Lorber M, Yoffe N, Scharf Y: Systemic lupus erythematosus: predisposition for uterine cervical dysplasia. *Lupus* 3:59-61, 1994
 46. Ruiz J, Sangro B, Cuende JI, Belouqui O, Riezu-Boj JI, Herrero JI, Prieto J: Hepatitis B and C viral infections in patients with hepatocellular carcinoma. *Hepatology* 16:637-641, 1992
 47. Adami H-O, Hsing AW, McLaughlin JK, Trichopoulos D, Hacker D, Ekblom A, Persson I: Alcoholism and liver cirrhosis in the etiology of primary liver cancer. *Int J Cancer* 51:898-902, 1992
 48. Schur PH: Clinical features of SLE. In: *Textbook of Rheumatology*. Edited by WN Kelley, ED Harris Jr, S Ruddy, CB Sledge. Philadelphia, WB Saunders, 1993